

### REMARKS

Attached hereto is a marked-up version of the changes made to the specification by the above amendment. The attached page is captioned “**Version with markings to show changes made.**”

Pursuant to 37 CFR 1.125(b), a substitute specification is hereby enclosed to make numerous typographical errors noted by the Examiner. Also enclosed is a marked up copy of the substitute specification as required by 37 CFR 1.125(b)(2). Pursuant to 37 CFR 1.125(b)(1), Applicants hereby state that the substitute specification contains no new matter. The substitute specification also contains the amendments submitted with the response filed August 15, 2001 (Paper No. 10), and entry is respectfully requested.

Claims 1-3, 5-7 have been amended to use alternate language directed to the same subject matter. The intended scope of the claims have not been narrowed, and support is provided at least by the claims and specification as originally presented.

No new matter has been introduced, and entry is respectfully requested.

As an initial matter, Applicants acknowledge the withdrawal of various requirements, objections, and rejections that were previously asserted.

#### ***Drawings***

Applicants acknowledge that Figure 1 remains objected to because “the picture covers the label identifying the drawings” but formal correction is held in abeyance pending indication of allowance of the instant application.

#### ***Specification***

In light of the numerous typographical errors, many of which occur in a single line, Applicants have submitted a substitute specification pursuant to 37 CFR 1.125(b) as noted above. The errors arose due to a printer malfunction. The substitute specification no longer contains italicized text in a subscript format.

The substitute specification also makes appropriate corrections for typographical errors on pages 3 and 10 as noted by the Examiner.

The substitute specification also includes deletion of "http://" from the text of the application. Applicants respectfully submit that this is fully responsive to the instant Office Action because there is no attempt to incorporate essential material into the instant application by reference to a hyperlink or other form of browser-executable code. Withdrawal of the objection to the specification is respectfully requested.

***Rejection under 35 U.S.C. § 112***

Claims 1-16 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite due to the phrase "effective amounts" in claims 1-3. Applicants respectfully traverse.

A simple review of claims 1-3 clearly indicate that the methods encompassed are directed to the effective treatment, prevention, or inhibition of various tumors. As such, the scope of the invention is clear to the ordinary artisan, who, in combination with the specification as filed, would recognize the scope of the claims. In the interest of advancing prosecution, however, and because it merely uses alternate phrasing without altering the intended scope of the claims, claims 1-3 have been amended as noted above. Applicants respectfully request that this rejection is misplaced, especially in light of the claims as amended, and request its withdrawal.

Claims 1-16 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite due to the phrase "irradiating said subject with light absorbed by said photosensitizer". Applicants respectfully and strongly traverse.

A simple review of the application as filed and the area of technology to which it pertains reveals that the use of PDT in living subjects has included the administration of a photosensitizer to a subject followed by irradiation of the subject with light absorbed by the photosensitizer. It is known in the art that there are various wavelengths of light which pass through the outer layers of skin and into deeper tissues of an organism. Additionally, it is accepted in the art to generically referring to irradiation of a part of a subject as irradiating the subject.

One advantage of PDT is that neither photosensitizer alone or activating light alone cause significant damage to a subject undergoing treatment. Therefore, irradiation of a subject as a whole simply activates photosensitizers at locations where the photosensitizer is present. No

ambiguity is introduced by the phrase, and Applicants respectfully submit that the rejection is misplaced. Withdrawal of the rejection is respectfully requested.

Claims 1-16 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for failing to “recite a positive step that clearly relates back to the preamble of the claims.”

Applicants respectfully traverse because no basis is offered for the asserted requirement for such a “positive step” in the claims. Additionally, the claims as originally presented were clearly directed to methods for uses related to tumors such that skilled artisans in that field would be readily apprised of the scope of the claims and the intended invention. In the interest of advancing prosecution, however, and because it merely uses alternate phrasing without altering the intended scope of the claims, claims 1-3 have been amended as noted above. Applicants note that as recognized by the Supreme Court of the United States in *Hubbell v. United States* with respect to claim construction and file history estoppel,

“where the differences between the claim as made and as allowed consist of mere changes of expression, having substantially the same meaning, such changes, made to meet the views of the examiners, ought not to be permitted to defeat a meritorious claimant.”<sup>1</sup>

As noted above, the amendments to the claims reflect changes in expression made to meet the views of the Examiner without narrowing or otherwise altering the scope of the claims. Applicants respectfully request that this rejection is misplaced, especially in light of the claims as amended, and request its withdrawal.

Claims 1-16 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the phrase “a component derived from lipid A of a bacterial lipopolysaccharide” in claims 1-3.

Applicants respectfully traverse because the Action notes that the phrase is indicated by the specification as referring to a derivative of lipid A. As such, the claims are already clear to

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<sup>1</sup> 179 U.S. 77, 80, 21 S.Ct. 24, 25, 45 L.Ed. 95, 98 (U.S. 1900).

the skilled artisan regardless of the possible “other” interpretation offered by the Examiner. Nevertheless, and to advance prosecution, the language has been amended to refer to a “derivative of” lipid A. Applicants again note the Supreme Court’s view quoted above and request that this rejection be withdrawn.

Claims 1, 2, and 4-16 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the term “metastatic tumor”.

Applicants respectfully traverse because the instant specification is clearly directed to the treatment of metastatic tumors as opposed to pre-metastatic tumors. As noted in the previous response filed August 15, 2001 (Paper No. 10), claim 2 is directed to “preventing or inhibiting the development of metastatic tumors” which indicates that there was one or more pre-metastatic tumor present in the subject to be treated. The nature of the invention as encompassed by claim 2 is that any tumor cells with metastatic potential that have migrated away from the one or more pre-metastatic tumor may be targeted by the disclosed methods and prevented or inhibited from developing into a metastatic tumor. This point is even more strongly emphasized in claim 4, where the subject has already undergone cancer or tumor therapy, indicating the presence of tumors in the subject prior to application of the claimed methods. Applicants thus respectfully submit that the term, while broad, is not ambiguous to the skilled artisan, who is able to readily ascertain the scope of the invention.

The Action’s reference to Korbelik et al. (reference “U” cited with the Office Action mailed April 10, 2001) is not understood. The comments in Applicants’ previous response (filed August 15, 2001, Paper No. 10) simply pointed out that there is no disclosure of the tumors in the treated mice as being metastatic. Whether the EMT6 tumors used by Korbelik et al. are useful as a “stand in” for pulmonary metastasis appears immaterial because *there is no indication that the actual tumor used by Korbelik et al. is metastatic under their conditions*. Additionally, Applicants respectfully submit that there is no support provided for the proposition that EMT6 are used as alleged by the Examiner.

Applicants respectfully submit that no basis for indefiniteness is present, and the rejection may be properly withdrawn.

Claims 2, 4-7, and 10-15 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the phrase “a subject at risk for developing metastatic tumors”. Applicants respectfully traverse.

The basis of this rejection appears to be centered on a supposed need for a “requisite degree of risk”. This is simply misplaced because the application and rejected claims relate to preventing or inhibiting the development of metastatic tumors in a subject. Applicants respectfully point out that the skilled artisan practicing in the art relating to metastatic tumors is fully capable of determining when a risk of metastatic tumor development is present. Such determinations are simply made on a daily basis, especially in clinical settings, around the United States. Such determinations by skilled artisans are informed by substantial research and studies on tumors and the metastatic process as well as tumor pathology. The instant rejection thus lacks adequate support for asserting that such artisans would not be able to ascertain the “requisite degree of risk”.

Additionally, this rejection is misplaced with respect to claim 4, which is directed to methods relating to subjects who have previously undergone cancer or tumor therapy. Such individuals would clearly be under the guidance of a skilled practitioner who would assess the risk of metastatic tumors without undue difficulty.

Applicants therefore respectfully submit that the instant rejection is misplaced and should be withdrawn.

Claims 5-7 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the term “mg/kg”. Applicants strongly traverse because the term in claims 5-7 as dependent from claims 1-3 would be clearly understood by the skilled artisan as referring to milligrams of photosensitizer per kilogram of subject.

However, and in an effort to advance prosecution, the claims have been amended as noted above. Applicants again note the Supreme Court’s view quoted above and request that this rejection be withdrawn.

Claim 11 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicants strongly traverse because the claim as dependent from claims 1-3 would be clearly understood by the skilled artisan. However, and in an effort to advance prosecution,

the claims have been amended as noted above. Applicants again note the Supreme Court's view quoted above and request that this rejection be withdrawn.

Claim 15 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the term "improves". Applicants strongly traverse because the term is not used in isolation or as an abstraction, as suggested in the Action. To the contrary, the term is used in relation to "improves penetration" of light absorbed by the photosensitizer. This refers to a phenomenon known in the PDT art with respect to bleaching a target with one wavelength of light to prevent spurious absorption with a subsequent wavelength of light. The ability to prevent spurious absorption of a subsequent wavelength is the very act of improving penetration of said subsequent light, which is understood by the skilled artisan.

The misplaced nature of the instant rejection is further supported by a review of US Patent 6,071,944 as cited in the Action and the specification on pages 27-28, bridging paragraph. Applicants respectfully submit that the emphasis in the instant rejection concerning "requisite degree" of improvement is misplaced because a broad range of improvement in penetration is within the scope of the claim. As the Examiner is no doubt aware, breadth of the claim is not necessarily identical to indefiniteness. See MPEP 2173.04 and the cases cited therein. Applicants respectfully request that this rejection be withdrawn.

Claim 15 has also been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the phrase "with light of a wavelength which improves penetration of the absorbed light". Applicants strongly traverse.

The instant rejection states that "it is unclear to into what matter the claim requires the irradiation to improve penetration." Applicants respectfully point out that claim 15 is dependent from claims 1-3 which clearly recite that the irradiation is of a subject to whom/which a photosensitizer and immuno-adjuvant have been administered. As such, it would be quite clear to the skilled person that claim 15 is directed to an improvement in penetration of the subject's cells and tissues. What else would it relate to?

The instant rejection also asserts that it is "unclear to what absorbed light the claim requires an improvement in penetration." Again, and with reference to claims 1-3, the skilled

person would recognize that it is the light absorbed by the photosensitizer that is being referred to. What else would it be?

The rejection also asserts that the wavelength of light which improves penetration is not recited in the claims and specification. Applicants again note US Patent 6,071,944 as cited in the Action and the bridging paragraph on pages 27-28 to support the position that such wavelengths of light are either known in the art or determinable without undue experimentation. As such, no issue of claim indefiniteness exists, and this rejection may be properly withdrawn.

***Prior art rejections under 35 U.S.C. § 103***

Claims 1-16 have been rejected under 35 U.S.C. § 103 as unpatentable over US Patent 6,290,712 B1 in view of US Patents 4,436,727; 4,912,094; 5,149,527; 5,579,554; 5,770,619; 5,929,105; 5,990,149; and 6,071,944 (hereafter the '712, '727, '094, '527, '554, '619, '105, '149 and '944 patents, respectively. Applicants have carefully reviewed the statement of the instant rejection as well as the cited reference and respectfully traverse the rejection as failing to have presented a *prima facie* case of obviousness.

As an initial matter, Applicants strongly traverse the assertion in the instant rejection that "the term 'malignant' is used to describe a tumor that is anaplastic, invasive, and metastatic" (see page 8 of the instant Office Action. A review of the '712 patent shows no support for such a definition. To the contrary, column 1, lines 24-27, specifically states that "malignant neoplasms, *most of which invade* surrounding tissues, *may metastasize* to several sites, and are likely to recur after attempted removal" (emphasis added). As such, the very art cited in the Action does not support the proposition that "malignant" in reference to a tumor or cancer necessarily indicates invasiveness or metastatic nature in all circumstances.

The instant rejection fails to present a *prima facie* case of obviousness for the following reasons:

--there is no expectation that green porphyrins would be effective in relation to metastatic tumors;

--there is no indication of functional equivalence, in relation to metastatic tumors, between the photothermal mediated effects of the '712 patent and the singlet oxygen mediated effects of "green porphyrin" mediated PDT of the instant invention; and

--there is insufficient motivation to combine the references.

Addressing these points in turn, Applicants first note that despite the large number of references cited, none of them teach or suggest the efficacy of green porphyrins with respect to metastatic tumors or metastasis in general. The instant rejection first discusses green porphyrins with reference to BPD and the '619 patent, but the patent does not even use the term "metastasis" or any derivative thereof.

Similarly, the '149 patent, relied upon with respect to BPD-MA, does not disclose or suggest the term "metastasis" or derivative thereof. Furthermore, the '105 patent, relied upon with respect to additional BPDs, is similarly deficient in this regard. As such, where is the expectation that green porphyrins would be effective with regard to metastatic tumors? Without such expectation in the art, the use of these references in combination with the '712 patent is based upon impermissible hindsight reconstruction of the claimed invention.

The remaining patents do not remedy this deficiency. The '727, '094, '527, and '554 relate to immuno adjuvants, and not to BPDs. And similar to the '619, '149, and '105 patents, the '944 patent does not even use the term "metastasis" or any derivative thereof. Moreover, none of these patents make any reference to secondary tumors. Therefore, there is no *prima facie* case of obviousness for failure to present a reasonable expectation of success. See MPEP 2143.02 and the cases cited therein.

Second, the cited patents do not provide any indication, suggestion or indication that the photothermal based effects seen in the '712 patent may be substituted with the singlet oxygen based effects of the present invention. This is important because the instant rejection asserts, without providing support, that "BPD has the ability to create thermal energy" (see Action on page 14). Without commenting on whether this may be accurate under some circumstances, it still does not address the issue of a reasonable expectation that a green porphyrin like BPD would be suitable for substitution in place of the agents used in the '712 patent. Again, no *prima facie* case of obviousness is present given the lack of recognition that a green porphyrin may be substituted into the methods of the '712 patent with a reasonable expectation of success.

Last, Applicants note that the last paragraph of the rejection sets forth the motivation for modifying the '712 patent disclosure as present in "a long-felt need at the time for more efficacious therapeutic means for treating, preventing, or inhibiting primary and secondary



cancers” (see page 16 of the Action). Multiple decisions, as noted in the MPEP at 2143.01, set forth the requirement that the motivation necessary to modify or combine references must relate to the claimed invention. The motivation presented in the instant rejection is so broad as to encompass every modification of the ‘712 patent in relation to primary and secondary cancers. This simply is not the standard for supporting a prima facie case of obviousness, and Applicants respectfully submit that this rejection should be withdrawn.

### Conclusion

In light of the above amendments and remarks, Applicant respectfully submits that claims 1-16 may be indicated as allowable, and early indication to that effect is urged. The Examiner is welcome to contact the undersigned if he determines that further discussions would prove useful.

In the event that the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 273012011100. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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## Version with markings to show changes made.

### In the Specification:

#### Kindly amend the Specification as follows:

Pursuant to 37 CFR 1.125(b), please substitute the enclosed substitute specification for the specification as originally filed.

### In the Claims:

#### Kindly amend the claims as follows:

1. (twice amended)                      A method of treating metastatic tumors in a subject, which method comprises:

administering to a subject afflicted by metastatic tumors effective amounts of a green porphyrin photosensitizer and an immuno-adjuvant, for treating metastatic tumors upon irradiation with light absorbed by said photosensitizer, wherein said immunoadjuvant is selected from the group consisting of mycobacterial cell wall skeletons and a [component derived from]derivative of lipid A of a bacterial lipopolysaccharide, and  
irradiating said subject with light absorbed by said photosensitizer,  
wherein said method is photochemical mediated photodynamic therapy (PDT) mediated treatment of said subject.

2. (twice amended)                      A method of preventing or inhibiting the development of metastatic tumors in a subject, which method comprises:

administering to a subject at risk for developing metastatic tumors effective amounts of a green porphyrin photosensitizer and an immuno-adjuvant, for preventing or inhibiting metastatic tumors upon irradiation with light absorbed by said photosensitizer, wherein said immunoadjuvant is selected from the group consisting of mycobacterial cell wall skeletons and a [component derived from]derivative of lipid A of a bacterial lipopolysaccharide, and  
irradiating said subject with light absorbed by the photosensitizer,

whereby the development of metastatic tumors in said subject is prevented or inhibited.

3. (twice amended)                      A method of treating a primary tumor in a subject, which method comprises:

administering to a subject clinically diagnosed with a primary tumor effective amounts of a green porphyrin photosensitizer and an immuno-adjuvant, for treating a primary tumor upon irradiation with light absorbed by said photosensitizer, wherein said immuno-adjuvant is selected from the group consisting of mycobacterial cell wall skeletons and a [component derived from]derivative of lipid A of a bacterial lipopolysaccharide, and  
irradiating said subject with light absorbed by said photosensitizer,  
whereby said method is photochemical mediated photodynamic therapy (PDT) mediated treatment of said subject.

5.(amended)                      The method of claims 1, 2 or 3 wherein said effective amount of a photosensitizer is in the range of 0.05 to 10 [mg/kg]milligrams of photosensitizer per kilogram of subject.

6.(amended)                      The method of claim 5 wherein said effective amount of a photosensitizer is in the range of 0.05 to 1 [mg/kg]milligrams of photosensitizer per kilogram of subject.

7.(amended)                      The method of claim 5 wherein said effective amount of a photosensitizer is in the range of 1 to 10 [mg/kg]milligrams of photosensitizer per kilogram of subject.

11.(amended)                      The method of claims 1, 2 or 3 wherein said photosensitizer is administered[,]to the subject and the subject irradiated[,]before administration of the immuno-adjuvant to the subject.